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The effect of captopril on renal function in patients during the first cis-diamminedichloroplatinum II infusion

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Summary. *On the assumption that hemodynamic changes in renal blood flow are the initial expression of cis-diammine-dichloroplatinum (CDDP)-related nephrotoxicity, we treated patients with metastatic non-seminomatous testicular carcinoma during CDDP infusion with captopril. This angiotensin-converting enzyme inhibitor significantly attenuated the initial decrease in effective renal plasma flow and can probably be used to protect the kidneys against CDDP-induced nephrotoxicity.*

Introduction

Cis-diamminedichloroplatinum II (CDDP) is an antitumor agent used in the treatment of a variety of malignancies [13, 14, 17]. Many side-effects are known [7], but the dose-limiting side-effect of CDDP is nephrotoxicity [8]. Adequate hydration and mannitol diuresis can prevent the decrease in renal function to some extent [2, 6], but there is still a considerable loss of renal function, reflected in a decrease in creatinine clearance or in glomerular filtration rate.

Meijer et al, have suggested primary changes in renal hemodynamics to be the cause of the platinum-induced nephrotoxicity [10]. Recently, by measuring effective renal plasma flow (ERPF) and glomerular filtration rate (GFR) during the first CDDP infusion, changes indicative of hemodynamic alterations in the kidney were also found [12].

The renin-angiotensin system plays an important role in changes in renal hemodynamics. To evaluate its role in CDDP-treated patients we performed renal function studies during CDDP infusion in patients also treated with an angiotensin-converting enzyme inhibitor. Captopril (S.Q. 14.225) was used as converting enzyme inhibitor and the possible protective effects of this agent on CDDP-induced nephrotoxicity were assessed.

Patients and methods

Twenty-two previously untreated patients with histologically proven disseminated non-seminomatous testicular cancer were studied. In this group the first 11 patients were treated with CDDP alone (group A). The next 11 patients also received captopril at a dose of 50 mg t. i. d. (group B). Captopril was started on day −1. There were no significant differences between the two groups. The mean age in group A was 31 years (21–48), and that in group B 28 years (18–52). The median ERPF and GFR before treatment are mentioned in Table 1 (ml/min).

All patients were treated according to the Einhorn regimen [4]. CDDP was given at a dose of 20 mg/m^2 over a period of 4 h in 500 ml NaCl 0.9%. All patients were normotensive, and no patients were subject to salt restriction. All patients were equally hydrated to procure a steady state of hydration, with 1 l of saline 0.9% every 3 h. This scheme started 12 h before renal function studies were performed and was maintained after the CDDP infusion. GFR and ERPF were measured three times before, four times during, and three times after the CDDP infusion. The values of pretreatment GFR and ERPF are the means of the three values before the CDDP infusion.

As described previously, glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) were measured with patients in the supine position with ^{125}I-sodium thalamate and ^{131}I-hippurate, respectively; errors in GFR introduced by

Table 1. Renal function changes during CDDP treatment without and with captopril

Patient no.	Group A				Patient no.	Group B			
	ERPF		GFR			ERPF		GFR	
	a	b	a	c		a	b	a	c
1	983	732	185	195	12	639	539	114	112
2	688	604	128	128	13	746	732	153	154
3	937	790	190	178	14	610	535	113	119
4	793	727	170	185	15	845	712	160	142
5	888	786	224	203	16	735	693	160	170
6	511	416	123	107	17	832	699	177	182
7	829	663	152	136	18	739	723	176	187
8	623	583	138	141	19	493	495	118	128
9	748	565	139	133	20	648	646	180	183
10	365	330	102	100	21	794	748	156	162
11	743	631	177	185	22	980	934	202	200
Median	748	631	152	141		739	699	160	162

a, Values before CDDP infusion
b, Nadir values of effective renal plasma flow during CDDP infusion
c, Values of glomerular filtration rate at time of the nadir values of ERPF
Group A, CDDP-treated patients without captopril
Group B, CDDP-treated patients also receiving captopril

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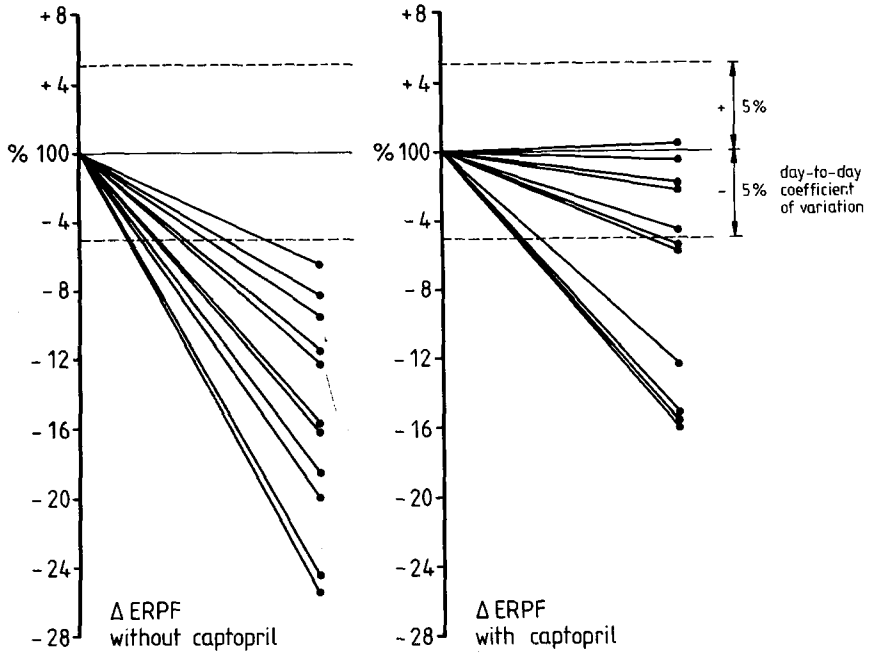

Fig. 1. Percentage change in effective renal plasma flow (ERPF) in a group of CDDP-treated patients without captopril and in a group of CDDP-treated patients also receiving captopril

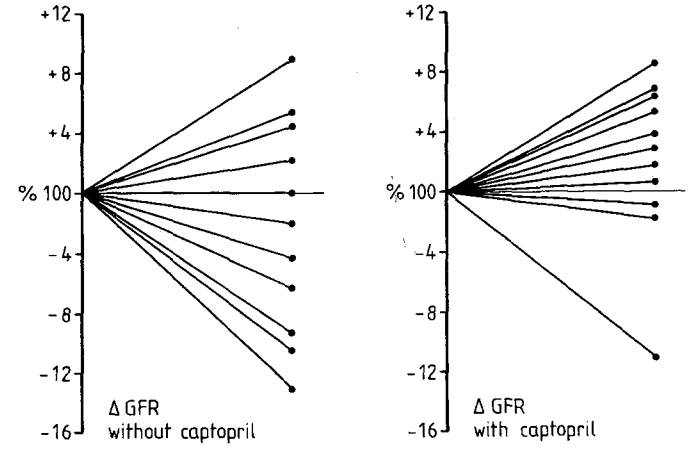

Fig. 2. Percentage change in glomerular filtration rate (GFR) in a group of CDDP-treated patients without captopril and in a group of CDDP-treated patients also receiving captopril

incomplete collection of urine were corrected; and the day-to-day coefficient of variation of the ERPF is $\leq 5\%$ and that of the GFR $\leq 2\%$ [3].

Statistics

Statistical analysis was performed with Wilcoxon's test for paired and unpaired observations (two-sided) and the two-by-two contingency tables (χ^2-test).

Results

In Table 1 the values of ERPF and GFR together with their medians are given for both the CDDP and the CDDP + captopril group. Mentioned are the pretreatment values and the nadir values of the ERPF with their corresponding GFR. The values are not corrected for body surface area. In Fig. 1 the relative changes in ERPF in both groups are given, and in Fig. 2 the relative changes in GFR.

In group A (platinum without captopril) a decrease in ERPF was found without a significant change in GFR. The median pretreatment ERPF fell in comparison to the median nadir ERPF from 748 to 631 ml/min (15.6%). The decrease (> 5% decrease) occurred in all 11 patients (100%, Fig. 1).

The nadir values of the ERPF in group B differed significantly from those in group A ($P < 0.02$). In group B (platinum with captopril) the decrease of the median pretreatment ERPF to the median nadir ERPF was from 739 to 699 ml/min, i.e., a decrease of 5.4% (Fig. 1). In contrast to group A, ERPF decreased (decrease > 5%) in only six of the 11 patients (54%, $P < 0.05$).

In neither groups was any significant change in glomerular filtration rate detectable (Fig. 2). Blood pressure remained normal throughout the study period in both groups. The captopril medication was well tolerated.

Discussion

In a previous study we found changes in renal function during CDDP infusion, consisting in a decrease in ERPF together with an increase in FF, with no change in GFR [12]. These findings suggested disturbances in renal hemodynamics as the initial expression of CDDP nephrotoxicity, in agreement with observations of Winston et al. [18]. Experimental work on acute renal failure induced by other heavy metals [5] seems to be compatible with these clinical observations.

It is tempting to relate these initial changes to the long-term effect of CDDP on renal function. Reduction of these initial changes, i.e., the decrease in ERPF, might prevent later impairment of renal function.

In attempts to elucidate the effect of CDDP on the kidney, an analogy is drawn with other heavy metals. In their study, Sraer et al. found a stimulation of intrarenal prostaglandin E_2 synthesis by mercuric chloride [16]. The same was found for uranyl nitrate [1]. Recently, an increased prostaglandin E_2 synthesis was found in CDDP-treated rats [11]. Schor et al. have studied the influence of prostaglandins on glomerular ultrafiltration [15]. They found that prostaglandins can lead to an increase in angiotensin II (A II) concentration through a stimulation of glomerular cAMP and renin. The role of the intrarenal renin-angiotensin system in the control of renal function has been explained by Levens et al. [9]. They reported

that A II can lead to a decrease in renal blood flow and a concomitant decrease in effective renal plasma flow [9].

Our hypothesis is that CDDP, by analogy with mercuric chloride, can lead to an increase in prostaglandin synthesis in the glomeruli, which leads in turn to a stimulation of the renin-angiotensin system and subsequently to a decrease in ERPF. Because the initial changes in ERPF during captopril infusion can be caused by stimulation of the renin-angiotensin system through stimulation of prostaglandin synthesis, we tried to prevent the initial decrease in ERPF by giving a converting enzyme inhibitor to CDDP-treated patients. However, it is also possible that other drugs, such as verapamil, could reduce the decrease in ERPF induced by CDDP.

In the present study we gave captopril, one of the angiotensin-converting enzyme inhibitors, to CDDP-treated patients and found a significantly less pronounced decrease in ERPF than in patients treated with CDDP without captopril.

The results of this study, in which captopril seems to reduce the initial decrease in ERPF significantly, is a further indication that a change in renal hemodynamics is an important pathogenetic mechanism in platinum-induced nephrotoxicity. Furthermore, the results are encouraging enough to justify a study of the value of continued captopril treatment in preventing long-term effects of CDDP on renal function.

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